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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,489	CANTOR, THOMAS L.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 60-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-18, 22-59, 81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-9, drawn to an isolated antibody, classified in class 530, subclass 387.2.

II. Claims 10-18, 22-59, 81, drawn to a method for measuring whole parathyroid hormone in a mammalian sample, classified in class 435, subclass 7.1.

III. Claims 60-65, 72-74, 78-80, drawn to an isolated parathyroid hormone, classified in class 435, subclass 335.

IV. Claims 66-71, 75-77, drawn to a multiple antigenic peptide, classified in class 436, subclass 547.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01).

In the instant case, the invention I, drawn to an isolated antibody, whereas invention III, drawn to an isolated parathyroid hormone, and invention IV, a multiple antigenic peptide comprising a branched oligolysine core conjugated with a plurality of the antigenic peptides. The three groups are structurally and functionally distinct. Thus, each invention possesses different modes of operation, different biological functions with different effects under MPEP §806.04.

2. Inventions I, III, IV and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products as recited in inventions I, III and IV can be practiced with another materially different product other than measuring the whole PTH

hormone in a test sample, such as isolation or purification of PTH hormones (invention I), or identifying PTH agonist or antagonist (invention IV), or purification or isolation of specific PTH fragments from test sample (invention V).

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, the search required for one group is not required for the other, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Mr. Cheng on 10/18/2004 a provisional election was made with traverse to prosecute the invention of group II, claims 10-18, 22-59 and 81. Affirmation of this election must be made by applicant in replying to this Office action.

5. Claims 1-9, 60-80 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 10-18, 22-30, 58-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5-26 of U.S. Patent No. 66895666. Although the conflicting claims are not identical, they are not patentably distinct from each other because the antibody used in the instant application specifically binds to the N-terminal sequence of the whole PTH, while more broadly defined than the antibody used in the issued claimed method of US 6689566, nevertheless an ordinary skilled person in the art would have recognized that the limitation of the issued claimed antibody specific binds to the initial N-terminal of PTH (SEQ ID No. 3) would encompass the claimed subject matter of the instant application.

Information Disclosure Statement

8. The information disclosure statement filed 3/1/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because foreign document DE 3347548 (German) is not coupled with an English translation. Furthermore, document US 60/224396 (Hammis et al.) is not a patent under inventor. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 112

Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 40-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The instant claims direct to a comparison in the form of a ratio or proportion between whole PTH (wPTH) level versus the combined C-terminal (c-PTH) fragment level and the mid-PTH (m-PTH) fragment levels, and refer a cutoff value to either adynamic bone disease or hyperparathyroidism.

In light of the specification, although applicant provides data in support of the recited claims, particularly in Table 2, it nevertheless imposes undue experimentation to one ordinary skill in the art as to the reliability and predictability of this information.

First, it is not known how many samples were involved in this experiment. Table 2 lists several related disease, such as adynamic bone disorder, mild hyperparathyroidism and severe hyperparathyroidism. Applicant also formulate a ratio, i.e. wPTH/cPTH and mPTH; or wPHT/cPTH-wPTH + mPTH-wPTH as a clinical indicator with respect to the foregoing mentioned disease. However, since the sample size is not known, it raises the concern of clinical reliability and predictability. For instance, how many samples are needed in order to conduct a statistically reliable model as recited by the applicant?

Furthermore, it is not clear what are the metes and bounds of each c-PTH or m-PTH used in Table 2. For instance, applicant defines C-terminal PTH to the "carboxy terminus of a PTH polypeptide having a free carboxyl group... a C-terminal PTH fragment refers to a non-whole contiguous portion of PTH having an intact C-terminal." (See section 0069) The term "mid-terminal PTH fragment" refers to a non-whole contiguous portion of PTH having neither an intact N-terminal nor an intact C-terminal. These types of PTH fragments may also be referred to herein as "mid-terminus fragments." (See Section 0070) Applicant further defines "[w]ithout being bound by theory, a mid-terminal PTH fragment does not include position 1, nor position 84 of said PTH.sub.1-84, but rather falls within these positions. (See Section 0079) In another word, the "m-PTH" covers 2-83 position, and the c-PTH covers position 1-83 (except 1-84would be an "intact" C-terminal; See Section 0069). It is therefore not clear what kind of c-PTH and –PTH applicant used to conduct the measurement, and whether the values, i.e. ratios, in Table 2 reflect to *all* the c-PTH and m-PTH fragments, and most importantly, whether all combinations of c-PTH or m-PTH with the w-PTH can accurately reflect different diseases status.

In view of the aforementioned lack of predictability in the art, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the recited method and absent working examples.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 10-18, 22-59, 81 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 10, it is not clear whether the recited method requires a radiolabeled or fluroesence labeled antibody to detect the binding of the complex.

With respect to claim 10, step (c), "assessing a complex formed" is vague and indefinite. It is not clear what step(s) constitutes "assessing". Furthermore, it is not clear whether this "assessing" step directly relates to the measurement of the level of the whole PTH.

With respect to claim 17, the claim language "comprising" is vague and indefinite. It is suggested applicant using "consisting' instead since comprising is an open language and the recited antibody may also bind to the whole 1-84 PTH.

With respect to claim 18, it is not clear whether the "at least four amino acids" are contiguous or simply randomly selected within the epitopes, such as human PTH_{1-8}, say amino acid 1, 6-8. Additionally, it is confusing because applicant further recites the binding between the antibody and the N-terminal sequence of whole PTH is dependent on the presence of amino acid residues 2-5 of the hPTH. Applicant needs to clarify.

With respect to claim 22, it is not clear why the non-whole PTH fragments is between PTH_{3-84} and PTH_{34-84} since 3-84 is overlapped with the N-terminal which is within the whole PTH region.

With respect to claim 33, it is not clear what is this PTH peptide, for instance, what is the metes and bounds.

With respect to claim 35, it is not clear what is the "mid-terminal PTH fragment". Applicant needs to specify its metes and bounds.

With respect to claim 35, it is not clear what is the C-terminal PTH fragment. Applicant needs to specify.

With respect to claim 35, it is not clear what is the N-terminal PTH fragment. Applicant needs to specify.

With respect to claim 81, it is not clear whether the recited unit is correct, i.e. pgm/ml. See Figure 5, the expression unit is pg/ml, not pgm/ml.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 10-18, 22-39, 58 and 81 rejected under 35 U.S.C. 102(b) as being anticipated by Slatopolsky et al. (Kidney Intl. 2000 58: 753-761).

Slatopolsky et al. teach a method of measuring a physiological level of whole parathyroid hormone in a mammalian sample. Slatopolsky et al. teach obtaining uremic patients blood samples, and using an antibody recognizing only the first six amino acids of the parathyroid hormone (PTH), i.e. N-terminal sequence, which would not bind to the non-whole PTH fragments, to determine binding as the level of the whole PTH in the patient's sample (See page 753, left column, fist paragraph; page 754, right column, Methods).

With respect to claims 11-18, the samples are from hyperparathyoid or renal transplant patients' blood (See page 754, right column, Method). The antibody could be monoclonal or polyclonal antibody (See Method). The antibody specifically binds to an epitope of PTH $_{1\text{-}6}$ (See Methods, page 753, left column, first paragraph).

With respect to claim 22-23, Slatopolsky et al. teach the non-whold PTH fragment, e.g. $PTH_{7\text{-}84}$ is within the range of $PTH_{3\text{-}84}$ and $PTH_{34\text{-}84}$ (See page 753, left column, third paragraph).

With respect to claim 24, Slatopolsky et al. teach using sandwich or competitive assay to determine the PTH level (See page 754, right column, Methods).

With respect to claims 25-30 and 33, Slatopolsky et al. teach using two antibodies, i.e. first for N-terminal $PTH_{1\text{-}6}$ and the second for $PTH_{7\text{-}84}$ which is a region other than the N-terminal, as capturing agents for whole PTH assay (see page 754, right column, Methods). The assay kit (i.e. Scantibodies laboratories, Santee CA) provides solid surface and biotin-avidin linker for the attachment of antibodies (See Methods).

With respect to claims 31-32, 81, Slatopolsky et al. shows that the level of parathyroid hormone in serum is around 344 pg/ml which is less than 4 pmol/L or within the range of 7 pg/ml to 39 pg/ml (See Figure 7, the whole PTH value ranging; page 758, left column, first paragraph).

With respect to claim 34, Slatopolksy et al. teach using antibody to measure $PTH_{7\text{-}84}$ peptide (See page 754, right column, Method).

With respect to claim 35, Slatopolksy et al. teach selected two parameters, i.e. whole TPH level and intact PTH level to in comparison of normal and patient serum sample (See Figure 10, note, total PTH level measured by I-Nichols assay).

With respect to claims 36-39, Slatopolksy et al. teach using the comparison, i.e. ratio of whole PTH versus total PTH, as a monitoring tool to determine bone turnover related disorder or hyperparathyrodism (See page 755, right column, Studies in vivo; Figure 6-10).

With respect to claim 58, Slatopolsky et al. teach the measurement of the level of whole PTH is useful for differentiating the normal PTH function and the hyperthyroidism (See page 753, right column, last paragraph).

15. Claims 10-18, 22-32, 58 and 81 rejected under 35 U.S.C. 102(b) as being anticipated by Gao et al. (J. Bone Mineral Res. 2001 16: 605)

Gao et al. teach a method of measuring a physiological level of whole parathyroid hormone in a mammalian sample. Gao et al. teach obtaining uremic patients blood samples, and using an antibody recognizing only the first four amino acids of the parathyroid hormone (PTH), i.e. N-terminal sequence, which would not bind to the non-whole PTH fragments, to determine binding as the level of the whole PTH in the patient's sample (See 606, left column, last paragraph; page 606, right column, first column).

With respect to claims 11-18, the samples are from hyperparathyoid or uremic patients' blood (See page 606, Materials and Method). The antibody could be monoclonal or polyclonal antibody (See Materials and Method). The antibody specifically binds to an epitope of PTH $_{1-4}$ (See Introduction, last paragraph).

With respect to claim 22-23 and 33, Gao et al. teach the non-whold PTH fragment, e.g. PTH_{7-84} is within the range of PTH_{3-84} and PTH_{34-84} (See page 606, right column, first paragraph).

With respect to claim 24, Gao et al. teach using sandwich or competitive assay to determine the PTH level (See Materials and Method).

With respect to claims 25-30, Gao et al. teach using two antibodies, i.e. first for N-terminal PTH_{1-4} and the second for PTH_{39-84} which is a region other than the N-terminal, as capturing agents for whole PTH assay (See Abstract; Method and Materials). The assay kit (i.e. Scantibodies laboratories, Santee CA) provides solid surface and biotin-avidin linker for the attachment of antibodies (See page 607, left column, first column).

With respect to claims 31-32, 81 Gao et al. shows that the level of parathyroid hormone in the serum is around 226 pg/ml which is less than 4 pmol/L and within the range of 8-37 pg/ml (See Table 1 and Table 2).

With respect to claim 34, Gao et al. teach using antibody to measure PTH_{39-84} peptide (See page 606, right column, Method).

With respect to claim 35, Gao et al. teach selected two parameters, i.e. whole TPH level and intact PTH level to in comparison of normal and patient serum sample (See page 606, Method and Figure 2; note, total PTH level measured by I-Nichols assay).

With respect to claims 36-39, Gao et al. teach using the comparison, i.e. ratio of whole PTH versus total PTH, as a monitoring tool to determine uremic patient (See page 611, Table 2; Figure 6-9).

With respect to claim 58, Gao et al. teach the measurement of the level of whole PTH is useful for differentiating the normal PTH function and the hyperthyroidism (See page 613, left column, first paragraph to right column, last paragraph).

Conclusion

16. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

January 3, 2005

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